AMERICAN ASSOCIATION OF POISON CONTROL CENTERS

3201 New Mexico Avenue • Suite 330 • Washington, DC 20016
Main 202-362-7217 • Fax 202-362-3240 • E-mail aapcc@poison.org
www.aapcc.org • www.1-800-222-1222.info

April 19, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Docket No. 81N-0050

This correspondence is the initial response to the letter of Curtis Rosebraugh, M.D., M.P.H., Division of OTC Drug Products, to the American Association of Poison Control Centers of September 15, 2003. Dr. Rosebraugh requested data from the American Association of Poison Control Centers, and the Toxic Exposure Surveillance System.

Enclosed is a copy of the final draft of the document "Guideline on the Use of Ipecac Syrup in the Out-of-Hospital Management of Ingested Poisons. This document has been submitted to the *Journal of Toxicology – Clinical Toxicology* for consideration of publication. The editor of the journal, the AAPCC President, and the Guidelines program coordinator are in agreement with the submission of this document to the FDA.

A second submission will follow, and respond to the remainder of the questions posed by Dr. Rosebraugh. I am,

Sincerely,

William A. Watson, PharmD, DABAT, FAACT, FCCP
Associate Director, Toxicosurveillance

Enc.
CC: J Youniss, MBA, Interim Executive Director, AAPCC
   D Borys, RPh, President, AAPCC

81N-0050   SUP1

Guideline on the Use of Ipecac Syrup in the Out-of-Hospital Management of Ingested Poisons[*]

Anthony S. Manoguerra, Pharm.D., DABAT, FAACT

Daniel J. Cobaugh, Pharm.D., DABAT

and

the Members of the Guidelines for the Management of Poisonings Consensus Panel

1

GUIDELINE SUMMARY

The use of gastric emptying techniques, including ipecac-induced emesis, in the management of poisoned patients has declined significantly in recent years. Historically, poison centers used ipecac syrup in two ways. Ipecac syrup was administered to patients prior to referral to the emergency department in attempts to start the gastric emptying process as early as possible. Additionally, poison centers used ipecac syrup in attempts to keep patients from requiring referral to medical facilities. In these situations, ipecac syrup was administered in the home and poison center staff performed follow-up telephone calls to gauge progress and outcome. Studies to determine the effectiveness of ipecac syrup demonstrate that it induces vomiting in a high percentage of people to whom it is administered and that it decreases the gastrointestinal absorption of ingested substances in a time-dependent fashion. However, the effectiveness of ipecac syrup in affecting patient outcome has not been studied in adequate clinical trials. Its effectiveness in preventing drug absorption has only been documented for a limited number of substances and is substantially reduced if it is given more than 30-90 minutes following ingestion of the toxic material. There are potentially significant contraindications, adverse effects and related problems associated with the use of ipecac syrup. It is the consensus of the panel that the circumstances in which ipecac-induced emesis is the appropriate or desired method of gastric decontamination are rare.

The panel concluded that the use of ipecac syrup might have an acceptable benefit-to-risk ratio in rare situations in which:

- there is no contraindication to the use of ipecac syrup; and

- there is substantial risk of serious toxicity to the victim; and

- there is no alternative therapy available or effective to decrease gastrointestinal absorption (e.g., activated charcoal); and

- there will be a delay of greater than 1 hour before the patient will arrive at an emergency medical facility and ipecac syrup can be administered within 30-90 minutes of the ingestion; and

- ipecac syrup administration will not adversely affect more definitive treatment that might be provided at a hospital.

In such circumstances, the administration of ipecac syrup should occur only in response to a specific recommendation from a poison center, emergency department physician, or other qualified medical personnel.

The panel decided not to address the issue of whether ipecac should remain a nonprescription, over-the-counter product. The panel does not support the routine stocking of ipecac in all households with young children but was unable to reach consensus on which households with young children might benefit from stocking ipecac. Instead, the panel concluded that individual practitioners and poison control centers are best able to determine the particular patient population, geographic and other variables that might influence the decision to recommend having ipecac on hand.

PREAMBLE

Historically, emetics have been commonly used in the treatment of ingested poisons. Zinc sulfate, copper sulfate, mustard powder, sodium chloride and extract of ipecacuanha have been advocated and used as emetics. The evidence of their efficacy

was the occurrence of vomiting. In 1822, Jukes (1) and Bush (2) independently published reports of the use of a new procedure called gastric lavage. This method of washing fluid into and out of the stomach through a tube became the standard procedure for treating poisoned patients. During the 19th and early 20th centuries, the use of ipecacuanha extract was discouraged because of the delay in onset of vomiting (3). In 1959, Arnold et al. (4) published the results of a study conducted in dogs that compared gastric lavage and ipecac-induced emesis in experimental salicylate poisoning. They demonstrated that emesis was more effective at removing an administered dose of sodium salicylate than was the lavage procedure used in the study. However, the authors also commented that "neither lavage or emesis under the most optimal conditions are consistent in their effectiveness, so that all patients after either form of therapy should be followed carefully for signs of drug intoxication...." In 1969, Boxer et al. (5) published what was considered by many to be the landmark study supporting the superiority of emesis over lavage. The authors reported that the amount of aspirin removed from the stomachs of aspirin-poisoned children was greater with ipecac-induced emesis than with gastric lavage. However, the amounts removed by both procedures were small and likely to be clinically insignificant. Following publication of this study, a period of ipecac use began that continued for several decades. The Food and Drug Administration approved ipecac syrup for over-the-counter sale in 1965 and poison centers and pediatricians have widely advocated its use since then. Only in the past 10-15 years has the effectiveness of all gastric emptying procedures been scrutinized.

Poison centers have used ipecac syrup in two ways. Ipecac syrup has been administered to patients prior to referral to the emergency department in order to start the gastric emptying process as early as possible. Robertson (6) demonstrated in 1962 that

the time from ingestion to emesis was 68.7 minutes if ipecac syrup was given in an emergency department whereas the time to emesis from administration of ipecac syrup outside the hospital was 18.7 minutes. He advocated the early administration of ipecac syrup, which led to poison centers encouraging the stocking of the drug in homes. Poison centers have also used ipecac syrup in order to keep patients from requiring referral to a medical facility. Ipecac-induced emesis was performed primarily in children who had ingested less than a serious amount of a toxic substance but an amount thought capable of producing symptoms. The ipecac syrup was administered and the child was left under the observation of a caretaker with frequent follow-up calls made by the poison center staff to determine the outcome and need for referral.

The Food and Drug Administration approved warnings for the labeling of ipecac syrup (Federal Register Volume 50: Number 10. Tuesday January 15, 1985) are:

- Do not use in persons who are not fully conscious.

- Do not use this product unless directed by a health professional. If turpentine, corrosives, such as alkalies (lye), strong acids or petroleum distillates, such as kerosene, paint thinner, cleaning fluid or furniture polish have been ingested.

Clinicians have expanded the contraindications for ipecac syrup (7) to include situations in which:

- the patient is comatose or has altered mental status and the risk of aspiration of stomach contents is high.

- the patient is having convulsions.

- the substance ingested is capable of causing altered mental status or convulsions.

- the substance ingested is a caustic or corrosive agent.

- the substance ingested is a low viscosity petroleum distillate with the potential for pulmonary aspiration and the development of chemical pneumonitis.

- the patient has a medical condition that may be exacerbated by vomiting (e.g., severe hypertension, bradycardia, hemorrhagic diathesis).

Ipecac syrup is now infrequently used in the treatment of poisoned patients in hospitals. The use of ipecac syrup recorded by poison centers peaked in 1985 and has declined substantially since then. Based on reports to the American Association of Poison Control Centers Toxic Exposure Surveillance System, ipecac syrup was used in 0.7% of exposures in 2001 compared to 15% in 1985 (8,9). In view of this declining use of ipecac, questions have arisen concerning the situations in which ipecac-induced emesis is appropriate. The purpose of this guideline is to provide assistance to poison center personnel in planning the role of ipecac syrup in the out-of-hospital management of poisoned patients.

METHODOLOGY

The methodology used for the preparation of this guideline was developed after reviewing the list of key elements of guidelines described by Shaneyfelt et al. (10). An expert consensus panel was established to oversee the guideline development process (see Appendix 1). To serve on the expert consensus panel, an individual had to have an exceptional track record in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant U.S. poison center experience, and be an opinion leader with broad esteem. A Specialist in Poison Information was also included as panel member. The American Association of Poison

Control Centers (AAPCC), the American Academy of Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT) chose members of their organizations to serve as panel members.

A search of the National Library of Medicine's MEDLINE database from 1966 through 2002 was conducted to identify articles related to this guideline. The MeSH heading "ipecac" was used for the search; no limits were applied. Bibliographies from several tertiary references were also reviewed to identify articles that were not found through the MEDLINE search. These references included *Goldfrank's Toxicologic Emergencies* (11), *Clinical Management of Poisoning and Drug Overdose* (12), *Ellenhorn's Medical Toxicology* (13), *Clinical Toxicology* (14), *Poisoning and Drug Overdose* (15), *Emergency Toxicology* (16) and *Poisindex* (17). The American Academy of Clinical Toxicology and European Association of Poisons Control Centres and Clinical Toxicologists Position Statement on Ipecac Syrup (18) was reviewed to identify other references. Only English language articles were retrieved. Articles were then categorized for review as efficacy studies, safety reports/studies, prevention program descriptions/studies, letters to the editor, selected general reviews. Each article was reviewed and abstracted by the authors of the guideline. Literature evidence was scored using a system based on a slightly modified version of the levels of evidence developed by the Centre for Evidence-Based Medicine at Oxford University (see Appendix 2) (19). Reviewed literature on the efficacy and safety of ipecac syrup-induced emesis with assigned levels of evidence is summarized in the evidence table created as part of this project. It is available electronically at http://www.aapcc.org/.

A draft guideline was prepared by the authors. The draft was submitted to the consensus panel for comment. Comments from the consensus panel members were

collected and addressed in a further revision of the guideline. External review of the second draft was conducted by distributing it electronically to AAPCC, AACT, and ACMT members and the secondary review panel. The secondary review panel consisted of representatives from the federal government, public health, emergency services, pediatrics, pharmacy practice, and consumer organizations (Appendix 3). Comments were submitted via a discussion thread on the public side of the AAPCC web site or privately via email communication to AAPCC staff. All comments were reviewed by the consensus panel and, when appropriate, addressed in the document. Following a meeting of the consensus panel, a third and final revision of the document was prepared and approved by the panel.

REVIEW OF EVIDENCE

The Frequency and Time to Emesis Following Ipecac Syrup Administration

A single dose of ipecac syrup has been shown to result in vomiting in 80-85% of patients. About 10-15% vomit after a second dose and 4-5% of patients fail to vomit even after a second dose (20-26). The type of drug ingested appears to play little role in determining the response to ipecac. Patients who have ingested drugs with antiemetic properties vomit with the same frequency as those ingesting other drugs (27,28).

The time from ipecac syrup administration to the onset of vomiting is consistently 15-30 minutes following a single dose and, in those patients requiring a second dose, vomiting usually occurs within 10 minutes of the administration of the second dose (21,24-26,28-34).

Twelve studies were reviewed in this category (6,20-28,35,36). Three of the studies were prospective clinical trials with evidence scores of 2b (21,23,35) while the others were case series with evidence scores of 4. However, the results of the clinical trials and the case series were comparable, reproducible and consistent and, therefore, the panel felt that the results were reliable.

The Amount of Material Removed by Ipecac-Induced Emesis - Animal Studies

Three studies using dogs as an experimental model determined that ipecac-induced emesis results in variable recovery of the experimental marker with a decline of recovery with time.

Arnold et al. (4) studied the removal of 500 mg/kg of sodium salicylate from the stomachs of 41 dogs given ipecac syrup at various times following salicylate administration ranging from 11 to 80 minutes. Recovery ranged from 4.3 to 75%; there was a poor correlation between the time of ipecac administration and the amount recovered. The animals that vomited spontaneously had an average recovery of aspirin of 24% while those given ipecac had an average recovery of 39%.

Abdallah and Tye (37) administered a barium meal to 28 dogs and then gave ipecac syrup at 0, 30 or 60 minutes after the meal. Emesis occurred an average of 46 minutes after ipecac administration. Recovery of barium was 62%, 44%, and 31% following ipecac administration at 0, 30 and 60 minutes, respectively.

Teshima et al. (38) administered ipecac syrup to four beagle dogs immediately after giving them acetaminophen, salicylic acid or kanamycin. The range of recovery of the markers was 42-65%.

The consensus panel determined that the ability to extrapolate these animal studies to humans was very limited and, therefore, no conclusions were based upon these studies.

The Amount of Material Removed by Ipecac-Induced Emesis—Volunteer Studies

Neuvonen et al. (29) administered ipecac syrup to six healthy volunteers either 5 or 30 minutes after being given acetaminophen, tetracycline or aminophylline in a crossover fashion. The area under the 24-hour serum drug concentration time curve was calculated. Ipecac given at 5 minutes reduced acetaminophen absorption by 65% but was no better than control at 30 minutes. Tetracycline absorption was reduced by 76% at 5 minutes and 30% at 30 minutes. Aminophylline absorption was reduced by 50% at 5 minutes but was no better than control at 30 minutes.

Neuvonen and Olkkola (30) gave cimetidine and pindolol to seven adult volunteers in a randomized, crossover study. Five minutes later, ipecac syrup or activated charcoal was administered. Cimetidine absorption was decreased by 25% with ipecac and pindolol absorption was decreased by 40%.

Tandberg et al. (39) administered 25 tablets of 100 µg cyanocobalamin to 18 adult volunteers in their crossover study. On one day they were given ipecac syrup and on the alternate day gastric lavage was performed. Both procedures were initiated 10 minutes after administration of the marker. Ipecac-induced emesis removed an average of 28% of the marker (range 6-70%).

The effect of ipecac-induced emesis on the absorption of tilidine was studied by Cordonnier et al. (40). Ipecac reduced the absorption of tilidine by 57% when given within 3 minutes of drug administration but had no effect when given at 25 minutes.

Ampicillin was used as a marker by Tennenbein et al. (41) in a four-limbed crossover study comparing untreated control, ipecac syrup, gastric lavage and activated charcoal in 10 adults. All interventions were performed 1 hour after administration of the marker. Emesis reduced ampicillin absorption by 38%.

In an attempt to quantify the maximum effectiveness of ipecac-induced emesis, Vasquez et al. (34) used radio-labeled sucralfate as a marker. Sucralfate is not absorbed from the stomach and does not affect normal gastric emptying time. Twenty volunteers received the marker followed by ipecac syrup at 5, 30 or 60 minutes. The average amount of the marker removed was 83% at 5 minutes, 59% at 30 minutes and 44% at 60 minutes.

Ten adults were given 3 g of acetaminophen by McNamara et al. (42) in a crossover study. One hour later they received no treatment, ipecac syrup or activated charcoal. Total absorption of acetaminophen was calculated by examining the area under the 8-hour serum concentration curve. The mean area under the curve was 21% lower for the ipecac group (94.32 μg hrs/mL) than for no treatment (119.41 μg hrs/mL).

Young and Bivens (32) administered 30 capsules containing Tc99m to 14 adults. Five minutes later, ipecac syrup was administered or gastric lavage performed. Emesis removed 54.1 ± 21.3% of the marker.

Twelve adults were given three 200-mg, sustained-release theophylline tablets and 16 barium sulfate tablets by Minton et al. (43). One hour later, in a randomized crossover fashion, subjects received no treatment, ipecac-induced emesis, gastric lavage

or activated charcoal. Barium tablets were recovered from seven of the 12 subjects treated with ipecac (range 2-15 tablets). There was no significant difference in plasma theophylline concentrations at all times measured for the untreated and emesis groups. The area under the concentration curve for the first 4 hours following no treatment and ipecac did not differ significantly.

Saincher et al. (33) examined the efficacy of ipecac during the first hour after ingestion in a crossover simulated acetaminophen overdose. Following administration of 3.9 g of acetaminophen, emesis was induced at 5, 30 or 60 minutes. Serum acetaminophen concentrations were measured at time 0, 30 minutes, 1, 2, 3, 4, 6 and 8 hours. Ipecac reduced acetaminophen bioavailability, as measured by the area under the concentration versus time curve, by an average of 67% when given at 5 minutes, at 30 minutes by 11% and at 1 hour by 21%. Only administration of ipecac 5 minutes after the acetaminophen dose differed significantly from untreated control.

Thirteen volunteer studies were reviewed and 10 have been described above. All were clinical trials (evidence ratings 1b or 2b). In each of these studies, a marker was given to either determine the extent of removal of material from the stomach or decreased absorption of the material following ipecac-induced emesis. Although these studies score well using the evidence-based scoring systems, there are a number of factors that might limit the extrapolation of the results of these studies to the clinical situation. As these were volunteer studies, the dose of material given needed to be sub-toxic. In all of the studies, volunteers were fasted prior to administration of the marker and induction of emesis. Both of these factors differ substantially from the typical poisoning situation. However, conclusions that can be drawn from these studies are that ipecac-induced emesis is most effective if given immediately after ingestion of the marker and

effectiveness in removal of the marker decreases rapidly in a time-dependent fashion. When ipecac syrup was given immediately after the marker, there was wide variability in removal of the material and, by 30 minutes after ingestion of the marker, ipecac-induced emesis was no better than untreated control.

The Amount of Material Removed by Ipecac-Induced Emesis—Clinical Studies Using Patients

Corby et al. (44) gave magnesium hydroxide to 29 children being treated for drug ingestion. The marker was given immediately prior to the use of ipecac or apomorphine to induce vomiting. Recovery of the marker from 13 children given ipecac ranged from 0% to 78% with a mean recovery of 28%. Auerbach et al. (31) performed a similar study using thiamine as a marker and comparing ipecac-induced emesis to gastric lavage. In the 51 adult patients given ipecac syrup, the recovery of the marker was $50 \pm 35\%$.

Saetta et al. (45) administered inert, barium-impregnated pellets to 60 poisoned patients just prior to administration of ipecac syrup, performance of gastric lavage or no treatment. In the 13 patients in the ipecac group, 58.5% of the pellets remained in the gastrointestinal tract with 39.3% of the pellets in the small bowel (compared to 16.3% in the untreated group). The authors concluded that emesis might force stomach contents into the small bowel. In another study by the same group, 13 overdose patients underwent endoscopy to determine residual gastric contents after ipecac-induced emesis. However, no quantification of the residual was performed and the number of tablets ingested was based on the history provided by the patient (46).

Amitai et al. (47) studied 50 children with acetaminophen ingestions reported to be greater than 100 mg/kg. The average time from ingestion to emesis was 78 minutes with a range of 15 to 235 minutes. Plasma acetaminophen concentrations were predicted using "standard pharmacokinetic parameters." Children who vomited within 60 minutes of ingestion had plasma concentrations that were 77% lower than predicted while those who vomited after 60 minutes had plasma concentrations 40% lower than predicted. The only factor used in the calculation of the predicted acetaminophen concentration was the dose ingested, which was estimated by the caregiver. Even though the authors attempted to explain how this would not have adversely affected the results, the accuracy of such estimations is highly suspect.

Underhill et al. (48) examined 60 patients admitted to an emergency department within 4 hours of an acetaminophen ingestion. Patients were divided into four groups: no gastrointestinal decontamination, ipecac-induced emesis, gastric lavage and activated charcoal. Plasma acetaminophen concentrations were measured at time 0, 60, 90 and 150 minutes after treatment and the effect of the treatment on the rate of decline in the levels was determined as measured by the difference between the first and last plasma concentration. The authors reported that the mean percentage fall between the first and last acetaminophen levels was 40.7% ± 18.3%. However, the first blood samples for all treatment groups as well as the control group were drawn at different times after ingestion of acetaminophen making comparison between the groups impossible. The average time from ingestion to first plasma concentration in the control group was approximately 70 minutes while in the ipecac group it was 120 minutes.

Bond et al. (49) reviewed records of 455 patients from 11 poison centers who had ingested acetaminophen. Of these, 85 patients received no gastrointestinal

decontamination and served as control. Ipecac syrup was given to 370 patients. The mean serum acetaminophen concentration in the control group was 33.1 ± 35.6 µg/dL. If ipecac-induced emesis occurred within 30 minutes of ingestion, the mean serum concentration was 16.6 ± 18.6 µg/mL; with emesis between 35 and 59 minutes, the mean serum concentration was 15.7 ± 21.5 µg/mL; between 60 and 89 minutes levels – 19.9 ± 21.4 µg/mL; between 90 and 120 minutes – 26.0 ± 27.5 µg/mL; and with emesis occurring more than 120 minutes after ingestion, the mean serum concentration was 31.1 ± 38.2 µg/mL. The authors concluded that when emesis occurred within 90 minutes of ingestion, ipecac-induced emesis was able to significantly reduce serum acetaminophen concentrations. This paper, which is often cited as evidence of effectiveness of ipecac syrup if given within 30 minutes of ingestion, has a number of significant problems that substantially limit its usefulness. The information was collected from poison center records in a retrospective fashion. A large number of patients were excluded from the study (1636) because of incomplete records or if their acetaminophen level was drawn before 4 hours or after 4.5 hours of the reported time of ingestion. Heavy reliance was, therefore, placed upon the history of the amount ingested, the time of ingestion and the time of ipecac administration and emesis provided by the caller and recorded by the poison specialist in the record. In addition, there was no effort to determine if the control and the ipecac syrup treatment groups were comparable.

Seven studies were reviewed. Five were given an evidence rating of 2b and the other two were case series (evidence rating 4). All of the studies in this category have major methodological flaws that make firm conclusions difficult to formulate. There is an indication, only in acetaminophen ingestions, that administration of ipecac within 30

minutes of ingestion might decrease plasma acetaminophen concentrations. The clinical

significance of these reductions, however, cannot be determined from these studies.

Evidence of Ipecac-induced Emesis on Patient Outcome

Kulig et al. (50) compared ipecac-induced emesis plus activated charcoal and

cathartic vs. activated charcoal and cathartic in 476 alert and cooperative poisoned

patients. There was no difference in the rates of hospital admission (both about 7%) or

the proportions of patients who clinically deteriorated (1.4% vs. 0.8%). The criteria for

admission, however, are unclear. Even though 33 patients were admitted only five were

reported to have clinically deteriorated following their initial emergency department

presentation.

Albertson et al. (51) examined the effect of ipecac-induced emesis followed by

activated charcoal vs. activated charcoal alone in 200 patients. There was no statistically

significant difference in the rates of admission to the hospital between the two groups

(14% vs. 11%) or the time of discharge from the emergency department. The major

difference between the two groups was that the ipecac plus charcoal group had a 5.4%

incidence of complications while the charcoal group had a 0.9% incidence. Four patients

in the ipecac plus charcoal group aspirated gastric contents vs. none in the charcoal-only

group. However, three of the gastric aspiration patients had overdosed on cyclic

antidepressants, making them inappropriate candidates for ipecac-induced emesis.

Kornberg and Dolgin (52) gave children with a history of a poisoning ingestion

ipecac syrup followed by activated charcoal on odd-numbered days (n=32) or activated

charcoal alone on even-numbered days (n=38). Administration of ipecac prolonged the

time to administration of activated charcoal by an average of 100 minutes and increased the time to discharge from the emergency department by an average of 39 minutes. There was no statistically significant difference in the rates of hospitalization for the two groups (.09% in the emesis group and 0% in the charcoal group) and no difference in patient outcome.

Bond (53) performed a retrospective review of 55,436 poison center cases from seven poison centers. Ipecac use at home ranged from 0.6% to 22.1% and the percentage of patients referred to the hospital ranged from 8.6% to 20.1%. The author felt that there was a trend toward increased referrals to the hospital in those centers that used less ipecac at home; however, this was not true in all centers examined. For example, the center using ipecac the most (22.1%) had a referral rate of 8.8% while the center that used it the least (0.6%) had a referral rate of 20.1%. For the other 5 centers studied, there was no relationship. A center with a 10.7% rate of ipecac use had an 11.3% referral rate while one with 3.5% ipecac use had an 11.4% referral rate.

There is no published evidence that ipecac-induced emesis has a positive benefit on the outcome of poisoned patients in the hospital or out-of-hospital setting. None of the published studies was designed to answer this question.

Ipecac Syrup Safety

Adverse events with ipecac syrup are due primarily to the toxicity of the alkaloids emetine and cephaline (54) or from physical injury resulting from the act of vomiting. Experience with ipecac syrup safety can be categorized as adverse events following single doses of ipecac syrup or as toxicities associated with chronic administration in

patients with eating disorders and in children who are victims of malicious administration.

Wax et al. (55) prospectively randomized children who had ingested potentially toxic berries to an ipecac and home observation group or a home observation-only group. The ipecac group had substantially more vomiting (100% vs. 0%), more diarrhea (39% vs. 10%) and sedation (20% v. 4%) than the observation-only group.

In a 6-month poison center study involving 776 patients who received ipecac syrup at home, 9.4% experienced vomiting beyond 1 hour after ipecac administration (22). Another poison center study described a group of 211 patients treated at home with ipecac syrup (56). Following ipecac administration, 17.1% (n=25) of the patients experienced protracted vomiting. In 23 patients, vomiting continued beyond 1 hour and six patients experienced more than six episodes of emesis.

In a four-limb crossover volunteer study comparing ipecac dosages, the investigators reported that the number of emetic events ranged from 2 to14 and the duration of emesis ranging from 12 to 390 minutes (33). Two of 10 subjects in a volunteer study by McNamara et al. (42) became hyperemetic, defined as emesis beyond 2 hours after ipecac administration. One subject required intravenous fluid rehydration for orthostatic hypotension. Litovitz et al. (26), in a review of poison center cases, reported the adverse events following administration of ipecac to 105 children between 6 and 11 months of age compared to 302 children between 12 and 35 months of age who also received ipecac. 16.7% of children from 6 through 8 months of age and 33.3% of children from 9 through 11 months of age, experienced diarrhea after ipecac administration. Diarrhea occurred in 25.8% of children from 12 to 35 months of age. This study did not include a group of untreated patients that might serve as a control.

A review of 31 patients treated with ipecac syrup in an emergency department and 32 patients treated at home reported lethargy in 21% but the study did not have an untreated control group for comparison (57). In a poison center study designed to describe adverse effects following ipecac syrup administration, 11.6% of 146 ipecac-treated patients experienced atypical lethargy (i.e., sleep that did not occur during a usual nap or sleep time) compared to 3% of 99 patients who did not receive ipecac (p <0.05) (56).

Wrenn et al. (58) evaluated the use of ipecac by health care professionals based on a 1-year retrospective review of calls to a poison center. In the opinion of the authors, ipecac use was inappropriate in 20% of the cases in which it was used. Among adults, the most common contraindication was ingestion of a substance known to cause altered mental status. In a fatality involving a cyclic antidepressant, a patient had a rapid change in mental status following administration of ipecac syrup and subsequently vomited and aspirated gastric contents. In an isoniazid-poisoned patient treated with ipecac syrup, aspiration of gastric contents occurred when vomiting was followed by the onset of convulsions. Irritability/hyperactivity, fever and diaphoresis have also been described following administration of ipecac syrup (26,57).

Tandberg et al. (59) described a 24-year-old woman who developed a Mallory-Weiss tear following ipecac administration for a multiple drug ingestion. Wolowodiuk et al. (60) described a case in which ipecac syrup was administered to an 18-year-old woman who presented to the emergency department several hours after ingesting stimulants containing caffeine, ephedrine, and pseudoephedrine along with ethanol. She developed pneumomediastinum and retropneumoperitoneum after persistent vomiting in excess of 2 hours. Knight and Doucet (61) described a fatal case of a 2½-year-old boy

treated with ipecac syrup in an emergency department after a reported ingestion of chlorpheniramine. Post-mortem examination showed acute esophagitis and rupture of the fundus of the stomach. A 14-month-old girl was given ipecac syrup after being observed chewing on the leaves of an amaryllis plant (62). She experienced several initial episodes of vomiting but continued to vomit for 42 hours after ingestion. She was seen by her physician and sent home; however, during a subsequent return to the hospital, she experienced cardiopulmonary arrest and was declared dead after 40 minutes of resuscitative efforts. On post-mortem examination, the left pleural space contained 50 mL of bilious fluid as well as the stomach and pylorus, which had herniated through the esophageal hiatus in the diaphragm. Klein-Schwartz et al. (63) reported the death of an 84-year-old woman who was given ipecac syrup following the ingestion of boric acid. She vomited seven times over 3 hours. During the next 6 hours, she developed a hemiplegia and a decreased level of consciousness. Computerized tomography revealed an acute right intracerebral hemorrhage in the lateral area of the cerebral hemisphere and the temporal lobe.

There are case reports describing myopathy and cardiomyopathy following abuse of ipecac syrup in patients with anorexia nervosa and bulimia (64-81). In each of these cases, ipecac syrup was self-administered numerous times over a period of weeks to months. Four of the patients died (64,69,72,74).

Ipecac syrup has been implicated in Munchausen syndrome by proxy (82-90). In two cases, the patients died from the ipecac syrup administration (86,90) and in each of the other cases, the condition of the patient improved following the limiting of visits by caretakers who had been administering ipecac syrup to the victims.

SUMMARY OF THE QUALITY OF THE EVIDENCE

1.   Syrup of ipecac induces vomiting in almost all people to whom it is administered (Grade A evidence).

2.   Ipecac-induced emesis decreases the gastrointestinal absorption of ingested substances although to varying, unpredictable extents (Grade A and B evidence).

3.   The longer the interval between ingestion of the substance and the administration of ipecac syrup, the less the effect. This has been documented for a limited number of substances and the effectiveness in removing ingested materials declines rapidly with time and is substantially reduced after 30 to 90 minutes (Grade A, B and C evidence).

4.   The effectiveness of ipecac syrup in affecting patient outcome has not been studied in adequate clinical trials (No evidence).

5.   The rate of hospitalization of patients with moderate or severe poisonings in whom ipecac has been administered has not been studied (No evidence).

6.   The use of ipecac syrup to induce vomiting is associated with uncommon, serious adverse effects (Grade C evidence).

7.   Patients with eating disorders have abused ipecac syrup. This abuse has led to significant morbidity and mortality (Grade C evidence).

CONCLUSIONS OF THE CONSENSUS PANEL

The panel reached consensus that the circumstances in which ipecac-induced emesis is the appropriate or desired method of gastric decontamination are rare. The

panel concluded that the use of ipecac syrup might have an acceptable benefit-to-risk ratio in rare situations in which:

- there is no contraindication to the use of ipecac syrup; and

- there is substantial risk of serious toxicity to the victim; and

- there is no alternative therapy available or effective to decrease gastrointestinal absorption (e.g., activated charcoal); and

- there will be a delay of greater than 1 hour before the patient will arrive at an emergency medical facility and ipecac syrup can be administered within 30-90 minutes of the ingestion; and

- ipecac syrup administration will not adversely affect more definitive treatment that might be provided at a hospital.

In such circumstances, the administration of ipecac syrup should occur only in response to a specific recommendation from a poison center, emergency department physician or other qualified medical personnel.

The panel decided not to address the issue of whether ipecac should remain a nonprescription, over-the-counter product. The panel does not support the routine stocking of ipecac in all households with young children but was unable to reach consensus on which households with young children might benefit from stocking ipecac. Instead, the panel concluded that individual practitioners and poison control centers are best able to determine the particular patient population, geographic and other variables that might influence the decision to recommend having ipecac on hand.

REFERENCES

1.   Jukes, E. New Means of Extracting Opium etc. From the Stomach. London Med. Phys. J. **1822**, *48*, 384-389.

2.   Bush, F. On the Common Syringe with a Flexible Tube, as Applicable to the Removal of Opium and Other Poisons From the Stomach. London Med. Phys. J. **1822**, *48*, 218-220.

3.   White, W. *Materia Medica, Pharmacy, Pharmacology and Therapeutics*; J & A Churchill: London, 1892.

4.   Arnold, F; Hodges, J; Barta, R; Spector, S; Sunshine, I; Wedgwood, R. Evaluation of the Efficacy of Lavage and Induced Emesis in Treatment of Salicylate Poisoning. Pediatrics. **1959**, *23*, 286-301.

5.   Boxer, L.; Anderson, F.P.; Rowe, D.S. Comparison of Ipecac-Induced Emesis with Gastric Lavage in the Treatment of Acute Salicylate Ingestion. J. Pediatr. **1969**, *74* (5), 800-803.

6.   Robertson, W.O. Syrup of Ipecac. A Fast or Slow Emetic? Am. J. Dis. Child. **1962**, *103*, 136-139.

7.   Howland, M.A. Syrup of Ipecac. In *Goldfrank's Toxicologic Emergencies*, 7th Edition; Goldfrank, L.R.; Howland, M.A.; Flomenbaum, N.E.; Hoffman, R.S.; Lewin, L.S.; Nelson, L.S., Eds; McGraw-Hill: New York, 2002; 465-468.

8.   Litovitz, T.L.; Klein-Schwartz, W.; Rodgers, G.C., Jr.; Cobaugh, D.J.; Youniss, J.; Omslaer, J.C.; May, M.E.; Woolf, A.D.; Benson, B.E. 2001 Annual Report of

the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. **2002**, *20* (5), 391-452.

9. Litovitz, T.L.; Klein-Schwartz, W.; White, S.; Cobaugh, D.J.; Youniss, J.; Omslaer, J.C.; Drab, A.; Benson, B.E. 2000 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. **2001**, *19* (5), 337-395.

10. Shaneyfelt, T.M.; Mayo-Smith, M.F.; Rothwangl, J. Are Guidelines Following Guidelines? The Methodological Quality of Clinical Practice Guidelines in the Peer-Reviewed Medical Literature. JAMA **1999**, *281* (20), 1900-1905.

11. Goldfrank, L,R.; Flomenbaum, N.E.; Lewin, N.A,; Weisman, R.S.; Howland, M.A.; Hoffman, R.S., Eds. *Goldfrank's Toxicologic Emergencies*, 6th Edition; Appleton & Lange: Stamford, CT, 1998.

12. Haddad, L.M.; Shannon, M.W.; Winchester, J.F., Eds. *Clinical Management of Poisoning and Drug Overdose*, 3rd Edition; W.B. Saunders: Philadelphia, 1998.

13. Ellenhorn, M.J., Ed. *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*, 2nd Edition; Williams & Wilkins: Baltimore, 1997.

14. Ford, M.D.; Delaney, K.A.; Ling, L.J.; Erickson, T. *Clinical Toxicology*; W.B.Saunders: Philadelphia, 2000.

15. Olson, K.R., Ed. *Poisoning & Drug Overdose*, 3rd Edition; Appleton & Lange: Stamford, CT, 1999.

16. Viccellio, P. Ed. *Emergency Toxicology*, 2nd Edition; Lippincott-Raven: Philadelphia, 1998.

17.   Toll, L.L.; Hurlbut, K.M. *Poisindex System*; Micromedex: Greenwood Village, CO (Edition Expires August 2002).

18.   Krenzelok, E.P.; McGuigan, M.; Lheur, P. Position Statement: Ipecac Syrup. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. J. Toxicol. Clin. Toxicol. **1997**, *35* (7), 699-709.

19.   Woolf, S.H.; Battista, R.N.; Anderson, G.M.; Logan, A.G.; Wang, E. Assessing the Clinical Effectiveness of Preventive Maneuvers: Analytic Principles and Systematic Methods in Reviewing Evidence and Developing Clinical Practice Recommendations. A Report by the Canadian Task Force on the Periodic Health Examination. J. Clin. Epidemiol. **1990**, *43* (9), 891-905.

20.   Malcolm, S.B.; Kuzemko, J.A. Ipecac Syrup in Acute Poisoning in Children. Practitioner **1969**, *202* (211), 666-667

21.   MacLean, W.C., Jr. A Comparison of Ipecac Syrup and Apomorphine in the Immediate Treatment of Ingestion of Poisons. J. Pediatr. **1973**, *82* (1), 121-124.

22.   Veltri, J.C.; Temple, A.R. Telephone Management of Poisonings Using Syrup of Ipecac. Clin. Toxicol. **1976**, *9* (3), 407-417.

23.   Schofferman, J.A. A Clinical Comparison of Syrup of Ipecac and Apomorphine Use in Adults. JACEP **1976**, *5* (1), 22-25.

24.   Ilett, K.F.; Gibb, S.M.; Unsworth, R.W. Syrup of Ipecacuanha as an Emetic in Adults. Med. J. Aust. **1977**, *2* (3), 91-93.

25.   Krenzelok, E.P.; Dean, B.S. Syrup of Ipecac in Children Less Than One Year of Age. J. Toxicol. Clin. Toxicol. **1985**, *23* (2-3), 171-176.

26. Litovitz, T.L.; Klein-Schwartz, W.; Oderda, G.M.; Matyunas, N.J.; Wiley, S.; Gorman, R.L. Ipecac Administration in Children Younger Than 1 Year of Age. Pediatrics. **1985**, *76* (5), 761-764.

27. Thoman, M.E.; Verhulst, H.L. Ipecac Syrup in Antiemetic Ingestion. JAMA **1966**, *196* (5), 433-434.

28. Manoguerra, A.S.; Krenzelok, E.P. Rapid Emesis From High-Dose Ipecac Syrup in Adults and Children Intoxicated with Antiemetics or Other Drugs. Am. J. Hosp. Pharm. **1978**, *35* (11), 1360-1362.

29. Neuvonen, P.J.; Vartiainen, M.; Tokola, O. Comparison of Activated Charcoal and Ipecac Syrup in Prevention of Drug Absorption. Eur. J. Clin. Pharmacol. **1983**, *24* (4), 557-562.

30. Neuvonen, P.J.; Olkkola, K.T. Activated Charcoal and Syrup of Ipecac in Prevention of Cimetidine and Pindolol Absorption in Man after Administration of Metoclopramide as an Antiemetic Agent. J. Toxicol. Clin. Toxicol. **1984**, *22* (2), 103-114.

31. Auerbach, P.S.; Osterloh, J.; Braun, O.; Hu, P.; Geehr, E.C.; Kizer, K.W.; McKinney, H. Efficacy of Gastric Emptying: Gastric Lavage Versus Emesis Induced with Ipecac. Ann. Emerg. Med. **1986**, *15* (6), 692-698.

32. Young, W.F., Jr.; Bivins, H.G. Evaluation of Gastric Emptying Using Radionuclides: Gastric Lavage Versus Ipecac-Induced Emesis. Ann. Emerg. Med. **1993**, *22* (9), 1423-1427.

33. Saincher, A.; Sitar, D.S.; Tenenbein, M. Efficacy of Ipecac During the First Hour after Drug Ingestion in Human Volunteers. J. Toxicol. Clin. Toxicol. **1997**, *35* (6), 609-615.

34. Vasquez, T.E.; Evans, D.G.; Ashburn, W.L. Efficacy of Syrup of Ipecac-Induced Emesis for Emptying Gastric Contents. Clin. Nucl. Med. **1988**, *13* (9), 638-639.

35. Krenzelok, E.P.; Dean, B.S. Effectiveness of 15-Ml Versus 30-Ml Doses of Syrup of Ipecac in Children. Clin. Pharm. **1987**, *6* (9), 715-717.

36. Garrison, J.; Shepherd, G.; Huddleston, W.L.; Watson, W.A. Evaluation of the Time Frame for Home Ipecac Syrup Use When Not Kept in the Home. J. Toxicol. Clin. Toxicol. **2003**, *41* (3), 217-221.

37. Abdallah, A.H.; Tye, A. A Comparison of the Efficacy of Emetic Drugs and Stomach Lavage. Am. J. Dis. Child. **1967**, *113* (5), 571-575.

38. Teshima, D.; Suzuki, A.; Otsubo, K.; Higuchi, S.; Aoyama, T.; Shimozono, Y.; Saita, M.; Noda, K. Efficacy of Emetic and United State Pharmacopoeia Ipecac Syrup in Prevention of Drug Absorption. Chem. Pharm. Bull. (Tokyo). **1990**, *38* (8), 2242-2245.

39. Tandberg, D.; Diven, B.G.; McLeod, J.W. Ipecac-Induced Emesis Versus Gastric Lavage: A Controlled Study in Normal Adults. Am. J. Emerg. Med. **1986**, *4* (3), 205-209.

40. Cordonnier, J.; Van den Heede, M.; Heyndrickx, A.; Wennig, R. Disposition of Tilidine in a Fatal Poisoning in Man. J. Anal. Toxicol. **1987**, *11* (3), 105-109.

41. Tenenbein, M.; Cohen, S.; Sitar, D.S. Efficacy of Ipecac-Induced Emesis, Orogastric Lavage, and Activated Charcoal for Acute Drug Overdose. Ann. Emerg. Med. **1987**, *16* (8), 838-841.

42. McNamara, R.M.; Aaron, C.K.; Gemborys, M.; Davidheiser, S. Efficacy of Charcoal Cathartic Versus Ipecac in Reducing Serum Acetaminophen in a Simulated Overdose. Ann. Emerg. Med. **1989**, *18* (9), 934-938.

43. Minton, N.A.; Glucksman, E.; Henry, J.A. Prevention of Drug Absorption in Simulated Theophylline Overdose. Hum. Exp. Toxicol. **1995**, *14* (2), 170-174.

44. Corby, D.G.; Decker, W.J.; Moran, M.J.; Payne, C.E. Clinical Comparison of Pharmacologic Emetics in Children. Pediatrics **1968**, *42* (2), 361-364.

45. Saetta, J.P.; Quinton, D.N. Residual Gastric Content after Gastric Lavage and Ipecacuanha-Induced Emesis in Self-Poisoned Patients: an Endoscopic Study. J. R. Soc. Med. **1991**, *84* (1), 35-38.

46. Saetta, J.P.; Quinton, D.N. Residual Gastric Content after Gastric Lavage and Ipecacuanha-Induced Emesis in Self-Poisoned Patients: an Endoscopic Study. J. R. Soc. Med. **1991**, *84* (1), 35-38.

47. Amitai, Y.; Mitchell, A.A.; McGuigan, M.A.; Lovejoy, F.H., Jr. Ipecac-Induced Emesis and Reduction of Plasma Concentrations of Drugs Following Accidental Overdose in Children. Pediatrics **1987**, *80* (3), 364-367.

48. Underhill, T.J.; Greene, M.K.; Dove, A.F. A Comparison of the Efficacy of Gastric Lavage, Ipecacuanha and Activated Charcoal in the Emergency Management of Paracetamol Overdose. Arch. Emerg. Med. **1990**, *7* (3), 148-154.

49.   Bond, G.R.; Requa, R.K.; Krenzelok, E.P.; Normann, S.A.; Tendler, J.D.; Morris, C.L.; McCoy, D.J.; Thompson, M.W.; McCarthy, T.; Roblez, J.; et al. Influence of Time until Emesis on the Efficacy of Decontamination Using Acetaminophen as a Marker in a Pediatric Population. Ann. Emerg. Med. **1993**, *22* (9), 1403-1407.

50.   Kulig, K.; Bar-Or, D.; Cantrill, S.V.; Rosen, P.; Rumack, B.H. Management of Acutely Poisoned Patients without Gastric Emptying. Ann. Emerg. Med. **1985**, *14* (6), 562-567.

51.   Albertson, T.E.; Derlet, R.W.; Foulke, G.E.; Minguillon, M.C.; Tharratt, S.R. Superiority of Activated Charcoal Alone Compared with Ipecac and Activated Charcoal in the Treatment of Acute Toxic Ingestions. Ann. Emerg. Med. **1989**, *18* (1), 56-59.

52.   Kornberg, A.E.; Dolgin, J. Pediatric Ingestions: Charcoal Alone Versus Ipecac and Charcoal. Ann. Emerg. Med. **1991**, *20* (6), 648-651.

53.   Bond, G.R. Home Use of Syrup of Ipecac Is Associated with a Reduction in Pediatric Emergency Department Visits. Ann. Emerg. Med. **1995**, *25* (3), 338-343.

54.   Manno, B.R.; Manno, J.E. Toxicology of Ipecac: a Review. Clin. Toxicol. **1977**, *10* (2), 221-242.

55.   Wax, P.M.; Cobaugh, D.J.; Lawrence, R.A. Should Home Ipecac-Induced Emesis Be Routinely Recommended in the Management of Toxic Berry Ingestions? Vet. Hum. Toxicol. **1999**, *41* (6), 394-397.

56.   Czajka, P.A.; Russell, S.L. Nonemetic Effects of Ipecac Syrup. Pediatrics **1985**, *75* (6), 1101-1104.

57.   Chafee-Bahamon, C.; Lacouture, P.G.; Lovejoy, F.H., Jr. Risk Assessment of Ipecac in the Home. Pediatrics **1985**, *75* (6), 1105-1109.1.

58.   Wrenn, K.; Rodewald, L.; Dockstader, L. Potential Misuse of Ipecac. Ann. Emerg. Med. **1993**, *22* (9), 1408-1412.

59.   Tandberg, D.; Liechty, E.J.; Fishbein, D. Mallory-Weiss Syndrome: an Unusual Complication of Ipecac-Induced Emesis. Ann. Emerg. Med. **1981**, *10* (10), 521-523.

60.   Wolowodiuk, O.J.; McMicken, D.B.; O'Brien, P. Pneumomediastinum and Retropneumoperitoneum: an Unusual Complication of Syrup-of-Ipecac-Induced Emesis. Ann. Emerg. Med. **1984**, *13* (12), 1148-1151.

61.   Knight, K.M.; Doucet, H.J. Gastric Rupture and Death Caused by Ipecac Syrup. South. Med. J. **1987**, *80* (6), 786-787.

62.   Robertson, W.O. Syrup of Ipecac Associated Fatality: a Case Report. Vet. Hum. Toxicol. **1979**, *21* (2), 87-89.

63.   Klein-Schwartz, W.; Gorman, R.L.; Oderda, G.M.; Wedin, G.P.; Saggar, D. Ipecac Use in the Elderly: The Unanswered Question. Ann. Emerg. Med. **1984**, *13* (12), 1152-1154.

64.   Adler, A.G.; Walinsky, P.; Krall, R.A.; Cho, S.Y. Death Resulting From Ipecac Syrup Poisoning. JAMA **1980**, *243* (19), 1927-1928.

65.   Robertson, W.O. Safety of Ipecac Syrup. JAMA **1980**, *244* (15), 1675.

66. Brotman, M.C.; Forbath, N.; Garfinkel, P.E.; Humphrey, J.G. Myopathy Due to Ipecac Syrup Poisoning in a Patient with Anorexia Nervosa. Can. Med. Assoc. J. **1981**, *125* (5), 453-454.

67. Mateer, J.E.; Farrell, B.J.; Chou, S.S.; Gutmann, L. Reversible Ipecac Myopathy. Arch. Neurol. **1985**, *42* (2), 188-190.

68. Bennett, H.S.; Spiro, A.J.; Pollack, M.A.; Zucker, P. Ipecac-Induced Myopathy Simulating Dermatomyositis. Neurology. **1982**, *32* (1), 91-94.

69. Friedman, E.J. Death From Ipecac Intoxication in a Patient with Anorexia Nervosa. Am. J. Psychiatry **1984**, *141* (5), 702-703.

70. Moldawsky, R.J. Myopathy and Ipecac Abuse in a Bulimic Patient. Psychosomatics **1985**, *26* (5), 448-449.

71. Palmer, E.P.; Guay, A.T. Reversible Myopathy Secondary to Abuse of Ipecac in Patients with Major Eating Disorders. N. Engl. J. Med. **1985**, *313* (23), 1457-1459.

72. Dawson, J.A.; Yager, J. A Case of Abuse of Syrup of Ipecac Resulting in Death. J. Am. Coll. Health. **1986**, *34* (6), 280-282.

73. Rosenberg, N.L.; Ringel, S.P. Myopathy From Surreptitious Ipecac Ingestion. West. J. Med. **1986**, *145* (3), 386-388.

74. Schiff, R.J.; Wurzel, C.L.; Brunson, S.C.; Kasloff, I.; Nussbaum, M.P.; Frank, S.D. Death Due to Chronic Syrup of Ipecac Use in a Patient with Bulimia. Pediatrics **1986**, *78* (3), 412-416.

75. Friedman, A.G.; Seime, R.J.; Roberts, T.; Fremouw, W.J. Ipecac Abuse: a Serious Complication in Bulimia. Gen. Hosp. Psychiatry **1987**, *9* (3), 225-228.

76. Halbig, L.; Gutmann, L.; Goebel, H.H.; Brick, J.F.; Schochet, S. Ultrastructural Pathology in Emetine-Induced Myopathy. Acta Neuropathol. (Berl). **1988**, *75* (6), 577-582.

77. Kuntzer, T.; Bogousslavsky, J.; Deruaz, J.P.; Janzer, R.; Regli, F. Reversible Emetine-Induced Myopathy with Ecg Abnormalities: a Toxic Myopathy. J. Neurol. **1989**, *236* (4), 246-248.

78. Dresser, L.P.; Massey, E.W.; Johnson, E.E.; Bossen, E. Ipecac Myopathy and Cardiomyopathy. J. Neurol. Neurosurg. Psychiatry **1993**, *56* (5), 560-562.

79. Thyagarajan, D.; Day, B.J.; Wodak, J.; Gilligan, B.; Dennett, X. Emetine Myopathy in a Patient with an Eating Disorder. Med. J. Aust. **1993**, *159* (11-12), 757-760.

80. Ho, P.C.; Dweik, R.; Cohen, M.C. Rapidly Reversible Cardiomyopathy Associated with Chronic Ipecac Ingestion. Clin. Cardiol. **1998**, *21* (10), 780-783.

81. Cooper, C.; Kilham, H.; Ryan, M. Ipecac--a Substance of Abuse. Med. J. Aust. **1998**, *168* (2), 94-95.

82. McClung, H.J.; Murray, R.; Braden, N.J.; Fyda, J.; Myers, R.P.; Gutches, L. Intentional Ipecac Poisoning in Children. Am. J. Dis. Child. **1988**, *142* (6), 637-639.

83. Berkner, P.; Kastner, T.; Skolnick, L. Chronic Ipecac Poisoning in Infancy: a Case Report. Pediatrics **1988**, *82* (3), 384-386.

84. Sutphen, J.L.; Saulsbury, F.T. Intentional Ipecac Poisoning: Munchausen Syndrome by Proxy. Pediatrics **1988**, *82* (3 Pt 2), 453-456.

85. Colletti, R.B.; Wasserman, R.C. Recurrent Infantile Vomiting Due to Intentional Ipecac Poisoning. J. Pediatr. Gastroenterol. Nutr. **1989**, *8* (3), 394-396.

86. Day, L.; Kelly, C.; Reed, G.; Andersen, J.M.; Keljo, J.M. Fatal Cardiomyopathy: Suspected Child Abuse by Chronic Ipecac Administration. Vet. Hum. Toxicol. **1989**, *31* (3), 255-257.

87. Santangelo, W.C.; Richey, J.E.; Rivera, L.; Fordtran, J.S. Surreptitious Ipecac Administration Simulating Intestinal Pseudo-Obstruction. Ann. Intern. Med. **1989**, *110* (12), 1031-1032.

88. Johnson, J.E.; Carpenter, B.L.; Benton, J.; Cross, R.; Eaton, L.A., Jr.; Rhoads, J.M. Hemorrhagic Colitis and Pseudomelanosis Coli in Ipecac Ingestion by Proxy. J. Pediatr. Gastroenterol. Nutr. **1991**, *12* (4), 501-506.

89. Goebel, J.; Gremse, D.A.; Artman, M. Cardiomyopathy From Ipecac Administration in Munchausen Syndrome by Proxy. Pediatrics **1993**, *92* (4), 601-603.

90. Schneider, D.J.; Perez, A.; Knilamus, T.E.; Daniels, S.R.; Bove, K.E.; Bonnell, H. Clinical and Pathologic Aspects of Cardiomyopathy From Ipecac Administration in Munchausen's Syndrome by Proxy. Pediatrics **1996**, *97* (6 Pt 1), 902-906.